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# The Effect of Prenatal Administration of Amphetamine Upon the Cognitive-Intellectual Functioning of the Offspring at Adulthood

Theodore Cole

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THE EFFECT OF PRENATAL ADMINISTRATION OF  
AMPHETAMINE UPON THE COGNITIVE-INTELLECTUAL  
FUNCTIONING OF THE OFFSPRING AT ADULTHOOD

A Thesis

Presented to

the Faculty of the Department of Psychology

Western Kentucky University

Bowling Green, Kentucky

In Partial Fulfillment

of the Requirements for the Degree

Master of Arts

by

Theodore J. Cole

July 1978

The Effect of Prenatal Administration of Amphetamine  
Upon the Cognitive-Intellectual Functioning of the  
Offspring at Adulthood

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AMPHETAMINE UPON THE COGNITIVE-INTELLECTUAL  
FUNCTIONING OF THE OFFSPRING AT ADULTHOOD

Theodore J. Cole

July 1978

38 pages

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The effect of prenatal administration of amphetamine upon the offspring's cognitive-intellectual functioning at adult levels was investigated. Three groups of Max hooded rats were used, each composed of seven females and twelve males. One group was subjected to prenatal injections of amphetamine, one group received injections of saline, and the final group received no treatment. After the subjects reached adulthood they were presented with a series of complex mazes, and the dependent variable was the number of errors committed during the series. The data were analyzed by an analysis of variance of a 3 X 2 factorial design. The results indicated that there was a sex-specific response to the amphetamine and saline injections. These treatments significantly improved the performance of the males when compared to the no treatment males, but had no effect on the females. The amphetamine and saline injection produced the same effect as amphetamine on all subjects. Based on these results, an attempt was made to explain the mode of action of amphetamine and stress on the developing fetus.

## INTRODUCTION AND REVIEW OF THE LITERATURE

The prenatal environment of a developing fetus is subject to a wide variety of influences, and the importance of this environment upon the ontogeny of the offspring has long been recognized. In spite of this knowledge, two of the most common influences, drugs and stress, have been virtually ignored, except for studies of teratogenicity (whether or not a substance causes congenital deformations). This is particularly true of the stimulants, a class of drugs which is popular with a large segment of society in the form of coffee, tea, soft drinks, diet and pep pills. The most common drugs contained in these products are caffeine and amphetamine, which have similar biological and psychological effects (Leavitt, 1974; Valzelli, 1973).

Stress is a human universal, but its effects upon the developing fetus have also been virtually ignored by researchers. The studies which have been done tend to center around some physiological or motor activity and neglect the cognitive-intellectual components of the organism (Huttenen, 1971; Sobrian, 1976). This study was intended to address these problems by investigating the effects of prenatally administered amphetamine and stress upon the intellectual capabilities of the offspring. In order to conduct such an

investigation, the contributing variables must first be explored.

### Pregnancy

During pregnancy a single cell develops into an entire organism in a short period of time. In order to accomplish this, a unique environment is created within the female which is geared specifically for this task. The effects are not local, but involve the entire body of both the mother and fetus. There is a sensitive and complex series of hormonal changes which regulate this condition, and there are at least four mechanisms by which these hormones may effect the development of the fetus: 1) by directly stimulating the general somatic development of the tissues, 2) by bringing about differentiation and development of specific receptors, 3) indirectly activating some metabolic process necessary for prenatal development, and 4) by participating in fetal homeostasis, primarily in transplacental exchange (Delost, 1971).

As expected, the mother's endocrine system is greatly altered during pregnancy. In particular, the levels of estrogen, progesterone and adrenocortical hormones are elevated, and there is an increase in the cardiac output and in the basal metabolic rate (Cuyton, 1971). The fetus is also active in this process, as there is clear evidence that the fetus has a homeostatic mechanism of its own (Nesbitt, 1966), and that the maternal and fetal endocrine systems function in a complimentary fashion (Joffe, 1969).

The placenta is one of the most important organs during pregnancy. It is a membrane three cells thick which completely surrounds the fetus and is responsible for a number of functions. Its major task is to allow the diffusion of life-sustaining substances into the fetus' blood and the diffusion of waste products into the maternal blood (Guyton, 1971). To accomplish this, it has both simple diffusion and active transport systems (Hagerman, 1960). The rate of transport depends to a large degree on the lipid solubility of the substance transported, so that the blood-placenta barrier is much like the blood-brain barrier (Joffe, 1969).

Hormones such as the corticosteroids and thyroxine easily cross the placental barrier. Prolactin, corticotropin (ACTH) and somatotrophic hormone (STH) however, do not appear to be able to pass through the placenta. The estrogens, progesterone, prolactin, growth-hormone like factors, gonadotropin and androgens are able to pass through under certain circumstances (Delost, 1971), and it appears that nearly any drug or hormone administered to the mother will eventually reach the fetus (Hagerman, 1960; Joffe, 1969; Nesbitt, 1966; Werboff, 1963). All of this evidence indicates that the fetus and placenta must be regarded as an integrated endocrine unit which is able to manufacture and metabolize hormones (Delost, 1971), and that the administration of a factor which affects the endocrine system will surely affect the fetus and its development.

#### Stress and Stressors

According to Selye (1976), stress is a nonspecific

response of the body to any demand. Stress is therefore a state which affects all or most parts of an organism without selectivity, but which is indicated by a specific syndrome. This is called the General Adaptation Syndrome (Gas), and it is composed of three stages: alarm, resistance, and exhaustion.

In the alarm stage, the hypothalamus-pituitary-adrenocortical axis is activated. Stress signals reach the hypothalamus, which causes the pituitary to release ACTH. ACTH then stimulates the adrenal cortex to increase its secretions, which include aldosterone, corticosterone, deoxycorticosterone, cortisol, and cortisone. The first three of these increase the renal reabsorption of sodium while increasing the renal excretion of potassium. This leads to an increase in extracellular fluid volume, an increase in cardiac output, and moderate hypertension. Cortisol and cortisone increase the liver's production of glucose, increases the blood glucose level, mobilizes amino acids from the body tissues, increases the enzymes needed for protein metabolism, and mobilizes fatty acids (Guyton, 1971).

Stress also causes the adrenal medulla to increase its secretion of norepinephrine (NE) and epinephrine (E), which have widespread effects. These include an influence on the central nervous system (CNS), an increase in the basal metabolic rate and in mental activity, constriction of the blood vessels, an increase of the blood supply to tissues and an increase in the rate of fat mobilization. These changes, in turn, affect the rest of the endocrine system and apparently

mobilize every resource of the organism in order to cope with the stressful situation (Deutsch and Deutsch, 1973; Guyton, 1971; Selye, 1976). Since the entire organism is affected, the homeostatic balance of the fetal environment will also be affected. This new environment will contain an increased amount of corticosteroids, blood glucose, basic metabolic nutrients, and other hormones which are characteristic of a reaction to stress. It is assumed that the fetus will adapt to this situation, and that this process will alter the development and later behavior of the fetus.

#### Amphetamine

Amphetamine is a stimulant, and therefore has an excitatory effect on the organism. It does this by acting on the neuronal system in several ways: 1) it directly stimulates the catecholaminergic receptors, 2) it releases catecholamines, 3) it impairs the catecholamine reuptake mechanism, and 4) it partially inhibits monoamine oxidase activity (Cooper, Bloom and Roth, 1970; Groves and Rebec, 1976; Valzelli, 1973). Amphetamine crosses the blood-brain barrier very easily and reaches several brain structures in a short period of time (Valzelli, 1973). It affects the caudate and putamen, the cerebral cortex, hypothalamus, amygdala, and peripheral adrenergic terminals. It also causes the release of serotonin from the corpus striatum and dorsal raphe nucleus, and increases the brain levels of 5-hydroxyindole acetic acid (Groves and Rebec, 1976; Valzelli, 1973).

Since amphetamine affects a large number of structures, it is no surprise that amphetamine has a wide variety of



physiological, psychological and behavioral effects on an organism. These include a decrease in food consumption, mood elevation, an increase in motor activity with hyperthermia, mydriasis, vasoconstriction, tachycardia, bronchodilation, a decrease in the time spent in the deepest stage of sleep, increased muscle tonus, blood pressure and metabolic activity, an increase in blood constituents, blood urea and blood glucose, and a facilitation of intellectual and motor performance (Cole, 1967; Leavitt, 1974; Valzelli, 1973). Amphetamine is deactivated by the liver microsomal enzymes and by the granules in the sympathetic nerve terminals (Valzelli, 1973) and at normal doses amphetamine is behaviorally active for about four hours (Leavitt, 1974). It is thus apparent that amphetamine has a pervasive influence on both peripheral and central nervous system activity.

The effects of amphetamine as described above result in an alteration of the subject's homeostatic balance in the direction of excitation. This process also includes a change in the hormonal level of the mother, particularly of the stress hormones, and both of these processes effect the fetal environment. Furthermore, since amphetamine easily crosses the blood-brain barrier, and the placenta is very similar to the blood-brain barrier, it is assumed that amphetamine easily crosses the placenta and directly affects the fetus and its environment. It is assumed that the fetus will attempt to adapt to the new homeostatic balance, and that this process will affect the development and subsequent behavior of the fetus in the same manner as those organisms

exposed to stress.

### Stress, Drugs, and Pregnancy

In considering the effect of drugs and/or stress on the developing fetus, a large number of factors must be kept in mind. During the growth process, specific types of protein characteristics of the cells are formed which may be essential for the specific functioning of those cells. The structure of these proteins depend upon the activity of two regulatory mechanisms-genetic and enzyme.

In the genetic control mechanism, negative feedback in the form of a repressor substance acts directly on the DNA, resulting in an alteration of enzyme production. This regulatory system is especially important in controlling the intracellular level of amino acids and their derivatives and some of the intermediary substances of lipid, carbohydrate and protein metabolism (Guyton, 1971).

These regulatory mechanisms can produce a negative feedback system which can adapt a cell to its environment (Caspari, 1971). This regulation affects all of the cells of the body, and is particularly important in the CNS, in which the ordering of the neuronal pathways is essential for proper functioning of the organism. It is thought that this process is due to the presence of highly selective cytochemical affinities, with each cell having its own specific affinity for a particular tract or cell (Sperry, 1971). It is assumed that the morphological, functional and biochemical development of the cells of the CNS and endocrine glands

influence the functioning of the nervous system and behavior, particularly that of the organisms learning processes, (Caspari, 1971), and that this activity can be measured.

It also happens that many of the "stress hormones" are also important regulators of general growth, so that stress or drugs can effect the organism as a whole. These hormones affect the above regulatory mechanisms and it is therefore possible that the cell's affinity for the stress hormones may be altered by stress, with the result being a change in the homeostasis of the organism (Selye, 1976). This would consequently affect the functioning of the CNS by altering its functional, biochemical, and, perhaps, morphological properties resulting in a change in the organism's behavior. The other cells of the organism would also undergo similar changes in adapting to the fetal environment.

With the introduction of a stressor or drug, there are a large number of variables to be considered which have come from the areas of experimental teratology and genetics research. These variables include:

- 1) a factor may exert its effect on a developing structure up to the time of that structure's critical differentiation
- 2) in the course of development there exist critical periods, during which environmental factors can have substantial effects on the course of subsequent development
- 3) a single factor may cause a number of effects

- 4) a variety of factors may cause similar effects
- 5) artificially induced effects may be indistinguishable from naturally occurring effects
- 6) the effects of a single factor may vary with different species and with different genetic strains of the same species
- 7) most effects result from the interaction of genetic and environmental factors
- 8) factors can effect the activity of enzymes of differentiation specifically without any visible morphological effects
- 9) if tissue is developing along a path and is diverted by some factor, there is a strong tendency to return to that original path (canalization of development)
- 10) effects depend on the type and quantity of factor administered
- 11) effects vary with the period of pregnancy during which the factor is administered (Cohlan, 1964; Kretchmer, 1973; McClearn, 1969; Montagu, 1962).

There have been a number of studies which have investigated the above variables using amphetamine as the factor. Seliger (1971, 1973, 1975) has performed three experiments, each using essentially the same procedure. She injected groups of Gravid albino rats with either 5.0 or 10.0 mg/kg of amphetamine or with a control injection of saline. One injection was given each day and all were subcutaneous. The injections were made between days five and nine. This

covers the period of implantation and the beginning of embryonic differentiation (the time at which cells become specialized; that is, they become liver cells, nerve cells, etc.). The second group was injected between days twelve and sixteen of gestation, which covers the development of the CNS and the beginning of fetal motor movement. She began testing her subjects at day fifty-four post-partum. In one study, she found that all of the drug groups, except for the 5.0mg/kg at twelve-sixteen days, had significantly higher activity levels than controls (1971). However, in another study (1973), all drug groups except 5.0 mg/kg at five-nine days had higher activity levels.

Clark, Gorman and Vernadakis (1970) obtained different results than Seliger, but used a different strain of rats and a different method. Clark et.al. administered subcutaneous injections of 0.0, 1.0, or 3.0 mg/kg of amphetamine dissolved in a saline solution to Sprague-Dawley rats during days twelve through fifteen of gestation. They tested for motor activity at days thirteen, fifteen, eighteen, twenty-one, forty-six and sixty-six post-partum, and found that the amphetamine groups were significantly less active on day twenty-one. On day sixty, the control females were significantly more active than the control males, and the amphetamine females were more active than the males, but not significantly so.

Hitzemann, Hitzemann, Brase and Loh (1976) also used Sprague-Dawley rats, and also administered 0.0, 1.0, or 3.0

mg/kg of amphetamine subcutaneous to their subjects. However, they gave two injections per day, beginning at day five of gestation and continuing through the period of gestation. They reported that all of the amphetamine groups had increased motor activity levels.

All of the above studies indicate that the motor activity of the offspring was affected by prenatal exposure to amphetamine, but there is little consistency to the results. This inconsistency may be due to the time of gestation during which the factor is introduced, the amount administered, the length of the treatment, and the strain of animal used as subjects. Clark et.al. (1970) also seems to have found a sex-specific response to the treatment. Furthermore, their results indicate that the age of the offspring at testing may be an important variable. Seliger (1971, 1973) adds to the confusion by obtaining different results under the reportedly same experimental condition.

The offspring's response to an induced stress situation appear to be just as variable as measures of their motor activity. Bell, Drucker and Woodruff (1965) injected Long-Evans Hooded rats with 0.0 or 3.0 mg/kg of d-amphetamine dissolved in distilled water on day ten or day sixteen after being placed with a male. At forty-five days post-partum the offspring were subjected to a very stressful situation (taped down on their backs for forty-eight hours with no food or water). They found that the amphetamine groups were more emotional than the control groups.

Seliger (1971, 1975), using water-wading emotionality as her task, found that all of her amphetamine groups were more resistant to strong stress than the control animals. She concluded that this resistance was not a linear function of increased prenatal stress, but that moderate stress increased resistance while more or less stress had less beneficial effects. Bell et.al. differed from Seliger's treatment not only in the amount of induced prenatal stress, but also in the strain of animal used, the method of assessment used, the time and length of treatment, and the age at which testing began, all of which might influence the results.

Amphetamine also seems to alter the levels of the catecholamines of the brain when administered prenatally. Hitzemann et.al. (1976) discovered that on day thirty-five post-partum the brain level of norepinephrine (NE) in the amphetamine groups was decreased by twenty-one per cent. On day eighty-four, the NE levels were reduced by eighteen per cent in the diencephalon and brainstem, and the dopamine(D) levels were twenty-one per cent below normal in the brainstem.

Zemp and Middaugh (1975) obtained somewhat different results by administering amphetamine to C57Bl/Gl mice in doses of 0.0, 2.5, 5.0 and 10.0 mg/kg. The injections were given interperitoneally (IP) during the last trimester of pregnancy. They found that the amphetamine offspring had lower levels of brain NE at birth, but at day thirty the concentration of NE and D was higher than normals. This difference lasted until day seventy-five, at which time all groups had equal levels of NE and D. However, Zemp and Middaugh found that

when they repeated their experiment using sub-Q rather than IP injections, there were no differences between groups. It thus appears that, in addition to the above variables, the method of administration is also an important factor. This is further supported by Havlena and Werboff (1963).

One area of functioning that is almost totally ignored is the cognitive-intellectual abilities of the offspring. Seliger (1971, 1973) studied performance on a passive-avoidance task, but this was confounded by the subject's motor activity level. Clark et.al. (1970) tested the offspring for acquisition of a bar press response through operant conditioning beginning at twenty-seven days post-partum, and found no differences. They also tested the subjects in a simple T-maze task beginning at day thirty-three, and found no significant differences in T-maze acquisition, performance, reversals or errors between the groups. These tasks may have been too simple for the animals and were thus unable to distinguish between the groups. It is therefore the opinion of this author that the information regarding the effects of prenatal exposure to amphetamine upon intellectual functioning is insufficient and contributes little to our understanding of the situation. It was the purpose of this paper to investigate this area with a more rigorous test of the subject's cognitive-intellectual capabilities.

In order to assess any effect on the cognitive-intellectual processes, a measurement is required which is relatively free of confounding factors. Hebb and Williams (1946) and Rabinovitch and Rosvold (1951) have developed just



such a technique, which consists of a series of complex maze problems. This method virtually eliminates the factors of activity level and motivation, since the time to solution is not considered in the scoring.

This method also fulfills another attractive function in that it is an objective measure and provides a quantitative "IQ" score based on a series of observations (Hebb and Williams, 1946). Furthermore, this task has previously been used with success to distinguish between groups of animals which have undergone a variety of treatments which affect the cognitive-intellectual processes (Rabinovitch and Rosvold, 1951), so that it ideally suits the purpose of the present study.

## METHOD

### Subjects

Twenty adult female Max hooded rats were selected at random from the Western Kentucky University colony and divided into two numerically equal groups. Ten were randomly assigned to the experimental (E) groups, while the remainder constituted the control (C) group. All of these subjects were then paired for three days with randomly selected males for the purpose of impregnation.

### Procedure

After having been paired with a male for three days, the females were transported to Centre College in Danville, Kentucky, a trip of one hundred and seventy-five miles. The day that the females were separated from the males was designated day one of gestation, so that the trip to Danville occurred on day two of gestation.

Injections were begun at Centre College on day three of gestation and continued through day five, with one injection being given per day. The injections thus covered the period of implantation and the beginning of embryonic cellular differentiation (Seligier, 1971). All injections were administered subcutaneously and were given in the morning. During this time all of the subjects were housed in individual cages.

The experimental group received injections of five mg/kg body weight of d-amphetamine sulfate dissolved in a normal saline solution. The control group received an appropriate dose of the normal saline solution only.

All of the pups were born on the twenty-third or twenty-fifth day of gestation and were placed in maternity cages with the mother. At thirty days post-partum the mothers were removed and the pups were housed in group cages according to sex and litter.

There were a total of nineteen pups born to the experimental group, all of which were used in the testing procedure. The control group had more than nineteen pups; therefore, this group was reduced to match the experimental group as closely as possible on sex and litter size. Two weeks before testing, a no treatment (NT) group of nineteen subjects was selected from the colony. These subjects were also matched as closely as possible to the experimental group on sex and litter size. The final groups were each composed of seven females and twelve males, for a total of fifty-seven subjects.

The experimental procedure began when the experimental and control groups were one hundred five or one hundred seven days old. Due to the availability of subjects, the no treatment groups varied more widely in age.

#### Construction of the Apparatus

The closed-field apparatus was constructed according to the directions given by Rabinovitch and Rosvold (1951). The floor of the the box was composed of a 76.20 by 76.20 cm. piece of plywood, which was divided into thirty-six 12.70 by 12.70

cm. squares outlined in black. These lines defined the error zones and were the markers for the placement of the barriers. The walls were constructed from plywood and measured 10.16 cm in height. The barriers were constructed in the same way, and both the walls and barriers were painted black. Each barrier was nailed to a 5.08 by 0.95 cm. piece of sheet metal, which provided a base for stability. In addition, headless nails were placed on the tops of the barriers. These nails were then fastened to a screen which covered the entire maze to help prevent the barriers from shifting. The barriers were made in accordance with the following specifications: three barriers, each 12.70 cm. long; four 25.40 cm. long; three 38.10 cm. long; two 50.80 cm. long; two barriers 63.5 cm. long. Finally, an entrance alley was constructed at one corner, and a food compartment was placed at the opposite corner.

### Training

The preliminary training period was intended to acclimate the subjects to the apparatus, get them accustomed to eating at the food box, and to acquaint them with experimental procedure. In order to accomplish this, a series of six problems, A to F (See Figure 1), was used. These problems

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 Insert Figure 1 About Here  
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were administered in a sequential order until all six problems had been used, at which time the series was repeated. The

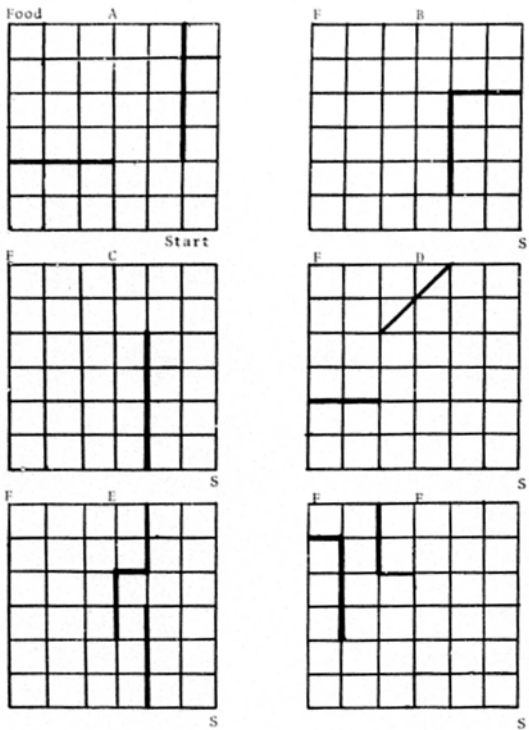


Figure 1. Floor plan of training problems

same problem was never presented twice in succession.

Before being placed in the apparatus for the first time, the subjects were deprived of food for twelve hours. All of the subjects in a single cage were placed in the apparatus at the same time and allowed to explore, eat, and drink in the box for ten minutes. At the end of this time they were removed to another cage to eat for an additional ten minutes. They were then placed back into their home cages until the next session. Once training had begun, the subjects had a constant water supply but were not fed in their home cages at any time.

The food consisted of moistened Purina rat chow mixed with sorghum, and, in addition, a sucrose solution was available at the goal box in the maze apparatus. Each subject was given two periods per day during all stages of the procedure, these beginning at seven a.m. and seven p.m.

As soon as the subjects appeared to have adapted to the box and were eating well, the preliminary trials were begun. Each subject was run individually for four trials per session until they could complete all of the runs within sixty seconds. Timing was begun when the subjects left the start box and ended when they reached the food container. At the end of each run the subjects were allowed to take a few bites of the food or a few sips of the sucrose solution before being replaced in the entrance alley for the next run. At the end of the four runs, the subjects were placed in a cage for approximately fifteen minutes in order to eat. These trials continued for all subjects until all of the subjects completed four trials within sixty seconds.

### Testing

Once all of the subjects had completed the training procedure, testing began with the twelve test problems (See Figure 2). One problem was presented at each trial until

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Insert Figure 2 About Here  
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all twelve problems had been given to each subject.

In each problem, the subject's score was the number of error zones entered. These zones are represented in Figure 2 by the dotted lines, and were counted when both of the subject's forefeet had crossed over one of the lines. Time for the runs was not measured and did not count in the scoring. As can be seen in Figure 2, some alleys contained more than one error zone. In this case, one error was scored for each error zone entered. No error was scored when the subject came out of an error zone, but if the subject re-entered an error zone an additional error was scored.

Each subject was given four trials per problem, so that each subject had a total of forty-eight trials for the entire series of twelve problems. The subject's final score was the total number of errors made on these forty-eight trials.

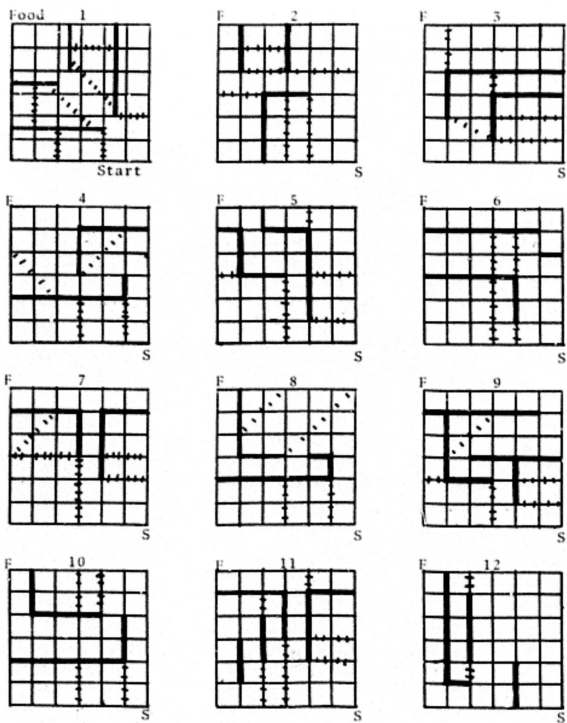


Figure 2. Floor plan of test problems



## RESULTS

The mean number of errors committed per animal for the twelve maze problems is presented by treatment and sex in Table 1. The second value in each quadrant is the standard

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Insert Table 1 About Here  
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deviation (SD) for the mean number of errors committed by the subjects. The values for the males show an increase in errors and in the SD as one goes from group E (92.58, 13.97) to group C (95.75, 16.85) to the NT group (123.58, 19.58). The females do not demonstrate such a pattern, the C group having the fewest number of errors (97.86) but the highest within group variability (17.03). It thus appears that the E group displays the least variability in the number of errors as measured by the SD, while the C and NT groups appear to be about equal on this measure. Both of the measures for the males and females of the E and C groups are very similar, while the NT group shows a larger discrepancy between the performance of the males and females.

The data were analyzed by an analysis of variance (ANOV), and the summary data for the treatment by sex (3X2) factorial design (Bruning and Kintz, 1977; Kirk, 1968) are contained in

Table 1  
Mean and Standard Deviation of Errors

Sex	Group		
	E	C	NT
Males	92.58, 13.97	95.75, 16.85	123.58, 19.58
Females	99.29, 12.05	97.86, 17.03	105.00, 14.02

Table 2. The effect of sex on performance was not signifi-

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 Insert Table 2 About Here  
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cant, but the treatment effect was highly significant,  $F(2,51)=8.95$ ;  $p<.005$ . The interaction between sex and treatment also had a significant effect on the number of errors made,  $F(2,51)=2.56$ ;  $p<.05$ , and this interaction is represented graphically in Figure 3. The divergence occurred with the NT group, in

-----  
 Insert Figure 3 About Here  
 -----

which the number of errors made by the males was far greater than the errors made by the females. The pattern of errors for males of the NT group are therefore a reversal from that of the E and C groups, in which the males had the fewer number of errors.

The interaction was analyzed with a Newman-Keuls' post-hoc comparison between all groups and subgroups. Table 3 summarizes the significant findings of this analysis. The

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 Insert Table 3 About Here  
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comparison of the main effects revealed that the E and C groups had committed significantly fewer errors than the NT group ( $p<.05$ ). However, an analysis of the interaction revealed that the NT males had made significantly more errors than any other subgroup. This contrasts with the performance of the NT females,

Table 2  
Analysis of Variance

<u>Source</u>	<u>SS</u>	<u>df</u>	<u>MS</u>	<u>F</u>
Sex (S)	124.47	1	124.47	0.42
Drug (D)	5305.92	2	2652.96	8.95*
S X D	1518.80	2	759.4	2.56**
Total	22041.99	56		
Error	15114.80	51	296.37	

\* $p < .005$

\*\* $p < .05$

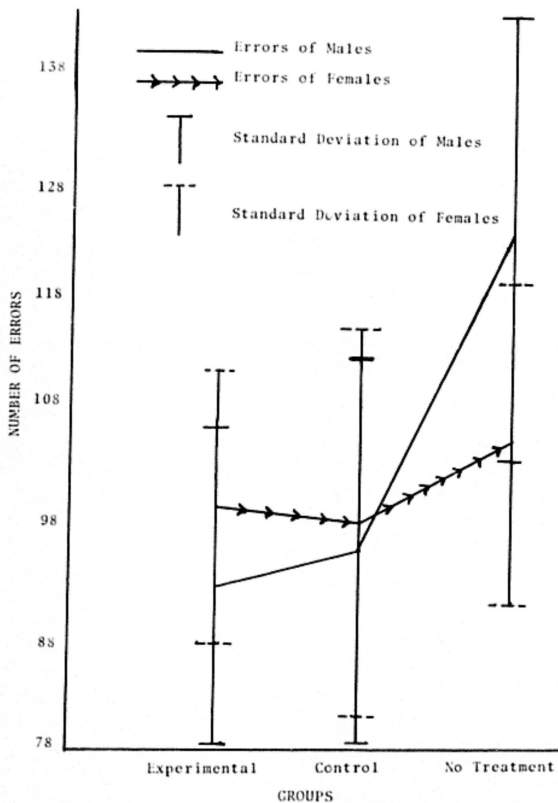


Figure 3. Means and standard deviations of errors

Table 3  
Newman-Keuls<sup>1</sup> Post-hoc Significant Comparisons

Comparison	r	Critical Difference	Difference
Comparison By Groups			
E <u>vs</u> NT	3	17.26	21.21
C <u>vs</u> NT	2	13.59	18.21
Comparison by Subgroups			
NT♂ <u>vs</u> E♂	6	29.18	30.25
NT♂ <u>vs</u> C♂	5	23.07	26.91
NT♂ <u>vs</u> E♀	3	19.64	23.54
NT♂ <u>vs</u> C♀	4	21.64	24.97
NT♂ <u>vs</u> NT♀	2	16.33	17.83

p < .05

who had more errors than the males and females of the E and C groups, but not significantly so.

#### DISCUSSION

The results indicate that the drug and/or stress factors had a significant effect upon the male subject's ability to perform on the maze task. There is also evidence for a numerical but not statistical effect for the females, which follows the same pattern as that of the scores for the males. It thus appears that the cognitive-intellectual capacities of the subjects were altered by these factors in a positive direction; that is, the subjects were able to perform better on a task requiring the use of these cognitive-intellectual traits than subjects who were not exposed to the drug/stress variables. The question is now one of discovering how this process occurs, and in response, the following model is presented to account for this situation.

According to the research noted in the Introduction, when a drug and/or stress factor is applied to an organism, it responds with the production of "stress hormones." These include norepinephrine (NE), epinephrine (E), and the corticosteroids (Selye, 1976), which produce an alteration in the homeostatic balance of the organism by accelerating the metabolism and preparing the animal to withstand the induced stress. This change affects the entire organism and every aspect of its functioning. In order to aid the system during this period, basic metabolic building blocks are released into the



bloodstream to be utilized for energy and structural strengthening/modification. During the process, the enzyme and/or genetic control mechanisms which regulate metabolic processes may be altered in order to meet the demands of the environment. This adaptation is accomplished through a change in cellular functioning and structure, particularly that of the membrane.

Concurrent with the alterations in the homeostasis of the organism is a change in the fetal environment, which reflects the condition of the mother. That is, all of the changes taking place in the mother's body directly or indirectly affect the growth and functioning of the fetus. One of these effects may be a change in the characteristics of the cellular membranes of the fetus, caused by the action of the stress hormones upon the metabolic regulatory mechanisms mentioned above. This change in the cellular membrane would affect the functioning of the cell by altering the membrane's affinity for the stress hormones, which occurs in order to adapt the organism to its environment. Since many of the stress hormones are also growth hormones, and since there is an increased availability of metabolic nutrients, one would also expect that the physical development of the fetus is superior to that of the normal fetus. The net result is that the fetus becomes geared for a stressful environment, and is able to withstand and function under stressful conditions as if they were "normal," and are superior to subjects not exposed to prenatal stress during "normal" conditions.

Perhaps one of the single most important effects of stress is that upon the noradrenergic system. Norepinephrine is both a peripheral and central neurotransmitter for the nervous system. Ascending pathways which utilize NE originate in the pons and medulla and project into the hypothalamus, the preoptic and septal areas, the amygdala, hippocampus, cingulate gyrus and neocortex (Deutsch and Deutsch, 1973; Valzelli, 1973). These structures are involved in the processes of emotion, learning, memory and arousal (Carlson, 1977; Deutsch and Deutsch, 1973), so that any change in the noradrenergic system produces changes in these areas. Both the present and previous studies indicate that drugs and/or stress increase the expression of these traits, so that an animal becomes more emotional, more aroused, and more intelligent. One way in which this may be accomplished is through the reduction of NE levels and alteration of the receptor site's membrane by the treatment (Hitzemann et.al., 1976; Zemp and Middaugh, 1975), which may alter the effects of NE on the above brain structures.

The results indicate that the drug and saline injected groups performed at the same level of ability on the maze problem, which suggests that stress alone is sufficient to produce the observed changes. However, the results can be interpreted in two ways. The first is Selye's contention (1976) that there is a single, unitary response of the organism to any stressor, which is the General Adaptation Syndrome. The important factor is not the direct effect of

the stressor upon the fetus, but rather it is the reaction of the mother and the subsequent biological alteration which is the crucial mediator of environmental factors and which causes the change in the growth and characteristics of the fetus. Thus, according to this hypothesis, any type of prenatal stress, including amphetamine, will have the same effect on the development and subsequent behavior of the organism.

The second possibility is that of similar effects caused by different factors (Cohlan, 1964), which means that the effects of different types of stress may appear to be the same but are actually different. In this study, the effects produced by the amphetamine injection on this task were the same as those produced by the saline injection, so that no differences were apparent between the two groups. However, differences may exist when a stress producing drug other than amphetamine is used.

There seems to be evidence in favor of both of these hypotheses. Data to support the "similar effects" concept come from Seliger (1971, 1973, 1975) and Hitzemann et.al. (1976), which suggest that amphetamine does have effects upon the fetus which are absent in subjects experiencing control injections. On the other hand, studies by Sobrian (1976) and Huttunen (1971) indicate that stress in the form of footshocks administered to the mother during gestation produces the same effects in the offspring as does amphetamine, thus supporting Selye's hypotheses.

The present study may be construed to support either of these hypotheses, since no differences were noted between the amphetamine and saline injection groups. However, the studies noted above used different strains and/or different types of measures to obtain their results, so that any differences may be accounted for by these variables. The complexity of obtaining results of this type is illustrated by Seliger (1971, 1973), who reported conflicting results derived from the use of the same procedure. Due to the small number of studies and the complexity of the variables involved in them, no decision as to the relative contributions of amphetamine and stress to the behavior of prenatally exposed offspring can be currently made.

The results of this study also indicate that there is a sex-specific reaction to prenatally administered stress. Both the amphetamine and saline injections significantly reduced the number of errors made by the males in the E and C groups when compared with the NT group males. The treatments did not, however, significantly change the performance of the females when compared with the NT group, although it did decrease the number of errors. In order to account for this difference, it is proposed that each subject has its own natural level of intelligence which is determined by the genetic make-up of the individual and the consequent effects on cellular structure and functioning. This level of intelligence can be affected by environmental factors through the processes, described previously, which alter the functioning of the organism.

There may be, however, limits on the change which can be produced in intelligence by the prenatal administration of amphetamine and/or stress. The females of the species used in this study appear to be able to function more effectively than males on the task. One possibility is that these females normally operate at the maximum level of intellectual change which can be accomplished by the methods used in this study. If this were true, the females would be unaffected by the procedure, while the males would display an improvement. This hypothesis is supported by the data of this study, in which the subjects followed this pattern of functioning.

This study indicates that the prenatal administration of amphetamine and/or stress produces an increase in cognitive-intellectual capacities. Previous studies indicate a variety of effects on other behaviors, and together they suggest that a number of factors interact with the experimental procedures. These include sex of the offspring, the period of gestation in which the drugs and/or stress are applied, the method of administration, the amount of stressor applied, and the duration of maternal exposure to these factors. The parameters of this type of intervention are poorly delineated, and deserve a thorough analysis to better understand and protect the development of the fetus.

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